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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,998	01/16/2007	Andrew Levy	P-7339-US1	1941

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,998	LEVY, ANDREW	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2009; March 1, 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1 and 15-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-14, 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 24, 2009 and March 1, 2010. Currently, claims 1-29 are pending. Claims 1, 15-28 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group IV, claims drawn to immunological kits in the paper filed March 1, 2010 is acknowledged. Applicants request rejoinder of the claims 8-11 in the event Claim 13-14 become allowable. The restriction requirement between the immunological kits and the nucleic acid kits has been withdrawn in view of the art cited.

Claims 1, 15-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 1 and 15-28 are drawn to an invention nonelected in the paper filed March 1, 2010. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

3. The information disclosure statement filed September 29, 2009 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

a. The IDS states that the references were filed in application 10/748,177. However, the '177 application is not related to the instant application by a claim of benefit under 35 U.S.C. 120. Therefore, copies of the documents must be filed in the instant application.

Priority

4. This application claims is a national stage application of PCT IL 04/01006, filed November 3, 2004.

Drawings

5. The drawings are acceptable.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2-14, 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a kit comprising reagents for determining haptoglobin phenotype of a diabetic patient and a kit with the intended use of determining a potential of a diabetic patient to benefit from vitamin E therapy for treatment of CV death or MI wherein the benefit from said vitamin E therapy to a patient having a haptolglogin 2-2 phenotype is greater compared to patients having haptoglobin 1-2 phenotype or 1-1 phenotype, does not reasonably provide enablement for a kit for determining a potential of a diabetic patient to benefit from any anti oxidant therapy for treatment of any vascular complication wherein the benefit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of determining a potential of a diabetic patient to benefit from anti oxidant therapy for treatment of a vascular complication by determining a haplotype phenotype of the diabetic patient and thereby determining the potential of the diabetic patient to benefit from said anti-oxidant therapy.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the art

The art teaches the effect of vitamin therapy on the progression of coronary artery atherosclerosis varies by haptoglobin type in postmenopausal women (Levy et al. Diabetes Care, Vol. 27, No. 4, pages 925-930, April 2004). Levy teaches that changes in the MLD as a function of haptoglobin phenotype and vitamin therapy were analyzed. The analysis of changes in LDL and HDL levels with and without vitamin therapy were analyzed in diabetic patients. The LDL levels in Diabetic patients was not significantly different between vitamin and placebo treated (see Table 4). Levy asserts that the benefit of antioxidant therapy with vitamin CX and E on progressive coronary artery stenosis may be restricted to woman with the Hp 1-1 phenotype 9page 927, col. 3).

Levy (Diabetes Care, Vol. 27, No. 11, pages 2767, November 2004) teaches "the absence of any statistical interaction indicates that these data do not support the hypothesis that the effects of vitamin E differed by Hp phenotype. Therefore, the results noted above in Hp 2-2 diabetic individuals demonstrating a significant reduction in CV death and myocardial infarction could be spurious and clearly require prospective testing in future trials." Thus Levy teaches the HOPE study cannot be relied upon, but rather replication is advised.

Levy (Pharmacology & Therapeutics, Vol. 112, pages 501-512, 2006) teaches atherosclerotic cardiovascular disease (CVD) was studied in determining whether antioxidant vitamin therapy may or may not be beneficial for a given patient with diabetes. Levy teaches there are a variety of antoxidants (vitamin E, vitamin C, folate, beta carotene, selenium, Q-10). Levy teaches vitamin E reduced CVD death and myocardial infarction in Hp 2-2 DM individuals in the HOPE study. However, no benefit was found from vitamin E supplementation in the diabetic cohort alone (page 510, col. 2). Levy teaches that there was no benefit observed in Hp 1-1 or Hp 2-1 individual with DM. Further, the WAVE and HPS studies did not find any benefit associated with antioxidant vitamin in the Hp 2 DM population. Levy suggests a 4-year double blinded clinical trial with 1500 Hp 2-2 DM individuals is being conducted in order to try to validate the findings presented above for Hp 2-2 DM individuals. Thus, it is clear that a single study show narrow results, but the results were not replicated in two additional studies.

The art teaches the effect of vitamin therapy on the progression of coronary artery atherosclerosis varies by haptoglobin type in postmenopausal women (Levy et al. Diabetes Care, Vol. 27, No. 4, pages 925-930, April 2004). Levy teaches that changes in the MLD as a function of haptoglobin phenotype and vitamin therapy were analyzed. The analysis of changes in LDL and HDL levels with and without vitamin therapy were analyzed in diabetic patients. The LDL levels in Diabetic patients was not significantly different between vitamin and placebo treated (see Table 4).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest

a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification and Working Examples

The specification provides no evidence that the broad scope of the claims are enabled. The specification has analyzed vitamin E and Ramipril which are deemed to be two particular anti-oxidant therapies. The specification teaches there is a 100% concordance between the haptoglobin phenotype as determined from plasma and the haptoglobin genotype as determined from genomic DNA by the PCR. As seen in Table 5 of the instant specification (page 45), the analysis based on DM patients only demonstrated a statistically significant result for Hp 2-2 phenotype in CV death and MI when treated with vitamin E. Table 6 illustrates that in diabetic patients the Hp 2-2 phenotype is not associated with CV death, MI or Stroke. The guidance provided by the

specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention as broadly as claimed.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

The claims are broadly drawn to any vascular complication, however, the specification fails to provide a significant association between CV, MI or stroke. Given the guidance in the instant specification it is clear that the skilled artisan would not be able to use the presence of the Hp 2-2 phenotype as indicative of CV, MI or stroke. The non-significant p-values provided for the analysis in the specification do not support a method for determining a potential of a diabetic patient to benefit from oxidant therapy. While the skilled artisan could provide additional experimentation to determine whether a subgroup of the population, or another population may have an association between hp 2-2 phenotype and all vascular diseases, the results are unpredictable, since three of the four complications studied did not yield positive associations.

Furthermore, given the analysis in the specification of vitamin E and Ramipril, there is no predictable correlation between Hp 2-2 phenotype and greater benefit for anti oxidant therapy. Diabetic patients with CV death and MI appear to be significantly associated with vitamin E. However, diabetic patients provided Vitamin E showed no association with stroke. The association pattern for Ramipril is different. CV death, MI and Stroke each do not appear to be significantly associated with Hp 2-2 phenotype in diabetics. Based upon the different patterns, the administration of one anti-oxidant therapy would not be indicative of each other anti-oxidant therapy. For example, since Vitamin E and Ramipril each have different associations, it would unpredictable whether

Vitamin C, for example, would be associated with anti oxidant therapy benefits. The specification does not provide any analysis for diabetic retinopathy, nephropathy or neuropathy, for example. Therefore, it would be unpredictable whether either Vitamin E, Vitamin C or Ramipril would be associated with Hp 2-2 phenotype and benefits from anti-oxidant therapy.

Finally, the study, as reviewed by Levy (2006) appears to be only one of 3 studies that was performed. No replication of the data was obtained in the additional studies in the WAVE or and HPS studies. The WAVE and HPS studies did not find any benefit associated with antioxidant vitamin in the Hp 2 DM population. In fact Levy suggests a 4-year double blinded clinical trial with 1500 Hp 2-2 DM individuals is being conducted in order to try to validate the findings presented above for Hp 2-2 DM individuals. Furthermore, Levy (Diabetes Care, Vol. 27, No. 11, pages 2767, November 2004) teaches "the absence of any statistical interaction indicates that these data do not support the hypothesis that the effects of vitamin E differed by Hp phenotype. Therefore, the results noted above in Hp 2-2 diabetic individuals demonstrating a significant reduction in CV death and myocardial infarction could be spurious and clearly require prospective testing in future trials." Thus, the art clearly teaches the need for replication and reliability.

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art do not provide a reliable association between anti oxidant therapies and benefits to vascular complications in diabetic patients. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems for association studies. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 2-14, 29 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Levy (US 6613,519, September 2, 2003).

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. With regard to the limitation that the kits contain instructions, the inclusion of instructions is not considered to provide a patentable limitation on the claims because the instructions merely represent a statement of intended use in the form of instructions in a kit. See In re Ngai, 367 F.3d 1336, 70 U.S.P.Q.2d 1862 (Fed. Cir. 2004)(holding that an inventor could not patent known kits by simply attaching new set of instructions to that product). Here, reagents for determining a haptoglobin phenotype meets this.

Levy teaches kit for evaluating a risk of a diabetic patient to develop cardiovascular disease (CVD). The kit comprises packaged reagents for determining a haptoglobin phenotype of the diabetic patient. Levy specifically outlines the hapltoglobin phenotyping protocol in Col. 17. Levy teaches methods using nucleic acids including ASO probes, PCR, CPR, DGGE/TGGE (limitations of Claims 7-11). Moreover, Levy teaches immunological detection methods such as ELISA and FACS (col. 14).

With respect to Claims 2-5, these limitations do not further limit the reagents in the kit, but limit the intended use. As noted above, intended use does not distinguish the prior art from the claimed invention.

Thus, Levy specifically teaches packaging reagents for determining a haptoglobin phenotype in a kit.

8. Claims 2-7, 12-14, 29 are rejected under 35 U.S.C. 102(b) as being anticipated by DeLanghe (WO 9837419, August 27, 1998).

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. With regard to the limitation that the kits contain instructions, the inclusion of instructions is not considered to provide a patentable limitation on the claims because the instructions merely represent a statement of intended use in the form of instructions in a kit. See In re Ngai, 367 F.3d 1336, 70 U.S.P.Q.2d 1862 (Fed. Cir. 2004)(holding that an inventor could not patent known kits by simply attaching new set of instructions to that product). Here, reagents for determining a haptoglobin phenotype meets this.

Delanghe teaches a method and kit for determining a haptoglobin phenotype and specifically relates to applications involving human haptoglobin. Delanghe in fact teaches a kit for determining the phenotype of a haptoglobin comprising a binding partner (see Claim 20)(limitations of Claims 12-14).

With respect to Claims 2-5, these limitations do not further limit the reagents in the kit, but limit the intended use. As noted above, intended use does not distinguish the prior art from the claimed invention.

Thus, DeLanghe specifically teaches packaging reagents for determining a haptoglobin phenotype in a kit.

Conclusion

9. No claims allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
May 17, 2010